REMARKS

A check for the fee for a three month extension of time accompanies this response. Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 06-1050. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 06-1050. A Supplemental Information Disclosure Statement is being filed on the same day herewith, under separate cover.

Claims 33-35, 39, 45, 46, 51, 52, 54, 55, 64, 65, 67-72, 74, 76, 77 and 78 are pending. Claims 33-35, 39, 45, 46, 51, 52, 64, 65, 67-72, 74, 75, 77 and 78 are amended for clarity. Claims 36-38, 40-44, 47, 53, 56-63, 66, 73, 76, 79-80 are cancelled without prejudice or disclaimer. Claims 51, 52, 64 and 65 are amended to correct claim dependency. The amendments find basis in the specification and claims as originally filed. For example, amendment of claim 33, finds basis in claims 34, 36-37 and 42-43 as previously pending.

As noted in the Office Action, the Examiner has agreed to defer any issues regarding obviousness-type double patenting with respect to co-pending Application No. 10/516,785 until there is allowable subject matter.

I. OBJECTION TO THE DRAWINGS

On page 3, the Office Action states that the Examiner is unsure if the drawings are color or black-and-white photographs and that the Applicant has not submitted a petition to enter color photographs. Applicant respectfully submits that the drawings are black-and-white photographs of *in vivo* imaging. Since they are black-and-white, no petition for color photographs is required.

II. OBJECTION TO CLAIM 80 UNDER 37 CFR §1.75(c)

Claim 80 is objected to under 37 CFR §1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim because it is alleged that claim 80 is limited to disorders or conditions which are no longer in the Markush group listed in the parent claim 35. Applicant respectfully disagrees. Nevertheless, in order to focus and advance prosecution, claim 80 is cancelled, rendering this objection moot.

Not withstanding argument, it respectfully is submitted that the test for proper dependence is **not** whether a claim further limits a base claim, but whether a dependent claim includes all limitations of the base claim. Attention is directed to MPEP 608.01(n), which defines the requisites for proper dependency of claims. The test for determining proper dependency of a claim is that:

> . . . it shall include every limitation of the claim from which it depends (35 U.S.C. 112, fourth paragraph) or in other words that it shall not conceivably be infringed by anything which would not also infringe the basic claim.
>
> A dependent claim does not lack compliance with 35 U.S.C. 112, fourth paragraph, simply because there is a question as to (1) the significance of the further limitation added by the dependent claim, or (2) whether the further limitation in fact changes the scope of the dependent claim from that of the claim from which it depends. The test for a proper dependent claim under the fourth paragraph of 35 U.S.C. 112 is whether the dependent claim includes every limitation of the claim from which it depends. The test is not one of whether the claims differ in scope. [emphasis added, see MPEP 608.01(n)].

Claim 80 included all limitations of the base claim. In addition, it respectfully is submitted that herniated nucleosis pulposis is a form of low back pain and Crohn's disease and ulcerative colitis are forms inflammatory bowel disease. Low back pain and inflammatory bowel disease are disorders or conditions listed in base claim 35 as filed. Hence, the rejected claim was not of improper dependent form.

III. REJECTION OF CLAIMS 61-63 UNDER 35 U.S.C. §101 FOR STATUTORY-TYPE DOUBLE-PATENTING

Claims 61, 62 and 63 are rejected under 35 U.S.C. §101 statutory-type double patenting as allegedly coextensive in scope with their respective base Claims 33, 34 and 35. Specifically, it is alleged that the rejected claims are "substantial duplicates" of the base claims because the recitation of detection by a signal does not further limit detection. It is alleged that "all detections are based on signals." While applicant does not concede that this rejection is correct, in view of the new Rules limiting applicant's ability to fully prosecute all issues, and in the interest of advancing prosecution to obtain allowance of claims, claims 61-63 are canceled herein, rendering this objection moot. Applicant, however, does not surrender any subject matter thereof.

IV. REJECTIONS OF CLAIMS 33-46 AND 51-80 UNDER 35 U.S.C. §112, FIRST PARAGRAPH – NEW MATTER

Claims 33-46 and 51-80 are rejected under 35 U.S.C. §112, first paragraph, as containing new matter. Various grounds of rejection are set forth, each of which are addressed in turn below.

A. Rejection of Claims 33-46 and 51-80 Under 35 U.S.C. §112, First Paragraph – New Matter

Claims 33-46 and 51-80 are rejected as containing new matter in the recitation of methods wherein the microorganism or cell does not contain a DNA encoding a protein that

produces or induces a detectable signal. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein . Without conceding the propriety of the rejection, claim 33 and claim 34 are amended to recited that the microorganism or cell encodes a detectable protein or a protein that induces a detectable signal, thereby obviating the rejection. The amendment is made to advance prosecution, not to limit the claims.

B. Rejection of Claims 35, 38, 39, 44, 47, 50, 53, 56, 63, 66, 73, 76, 79 and 80 Under 35 U.S.C. §112, First Paragraph – New Matter

Claims 35, 38, 39, 44, 47, 50, 53, 56, 63, 66, 73, 76, 79 and 80 are rejected as containing new matter because it is alleged that there is no basis for claims that recite diagnosis of low back pain *and* herniated nucleus pulposis because the specification and claims as originally filed allegedly only provide support for low back pain that is herniated nucleus pulposis. Without conceding the propriety of the rejection and in the interest of advancing prosecution, dependent claim 80 is cancelled, thereby obviating this rejection with respect to the pending claims.

V. REJECTION OF CLAIMS 35, 38, 39, 44, 47, 50, 53, 56, 63, 66, 73, 76, 79 and 80 UNDER 35 U.S.C. §112, FIRST PARAGRAPH –WRITTEN DESCRIPTION

Claims 35, 38, 39, 44, 47, 50, 53, 56, 63, 66, 73, 76, 79 and 80 are rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description because the claims encompass diagnosis and treatment, and the specification allegedly only describes the treatment and not the diagnosis of Crohn's disease, ulcerative colitis, atherosclerotic plaque, auto-immune disease, rheumatoid arthritis, multiple sclerosis, Alzheimer's disease, a fracture, an incision and a burn. This rejection respectfully is traversed insofar as it applies to amended claims 35 and 39. Claims 38, 44, 47, 50, 53, 56, 63, 66, 73, 76, 79 and 80 are cancelled herein, rending this ground of rejection moot with respect to these claims.

Relevant Law

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure. An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir. 1989).

The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also Ex parte Sorenson*, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a parent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application later can be amended to recite the function, theory or advantage without introducing prohibited new matter. *In re Reynolds*, 443, F.2d 384, 170 USPQ 94 (CCPA 1971); and *In re Smythe*, 480 F.2d 1376, 178 USPQ 279 (CCPA 1973).

The Rejected Claims

Claim 35 is directed to the method of claim 33, further comprising treating the subject for the detected wound, wounded tissue, inflammation site or inflamed tissue. Claim 39 recites that the treatment that is for an atherosclerotic plaque.

Claim 33 recites:

> A method for detecting the presence or absence of a wound, wounded tissue, an inflammation site or inflamed tissue, comprising:
>
> administering to a subject a bacterium, wherein the bacterium encodes a detectable protein or a protein that induces a detectable signal;
>
> monitoring the subject to detect the detectable protein or signal to detect accumulation of the bacterium at any wound, wounded tissue, inflammation site or inflamed tissue in the subject, thereby detecting the presence or absence of a wound, wounded tissue, an inflammation site or inflamed tissue in the subject, wherein:
>
> the subject is one who is being evaluated for the presence or absence of a wound, wounded tissue wound, an inflammation site or inflamed tissue;
>
> the bacterium is non-pathogenic or attenuated;
>
> the bacterium is recognized by the immune system of the subject; and
>
> the bacterium replicates in the subject.

Analysis

It respectfully is submitted that the specification describes detection of a wound, wounded tissue, inflammation site or inflamed tissue followed by administration of a treatment therefor. he specification describes, for example, at pages 6 and 7, paragraphs [0023] and [0024], preparation of microorganisms and cells to identify wounds, wounded tissues, inflammatory sites and inflamed tissue and to the effect treatment thereof. Paragraph [0024] includes the following recitation:

> Accordingly, the present invention relates to the use of a microorganism or cell containing a DNA sequence encoding a detectable protein or a protein capable of inducing a detectable signal for the preparation of a diagnostic composition for diagnosis and/or visualization of wounded or inflamed tissue or a disease associated therewith. In addition, said microorganism is also useful for therapy, since following visualization of wounded or inflamed tissue compounds suitable for therapy can be applied, *e.g.* by topical administration, such as, *e.g.*, acylated iridoid glycosides from Scrophularia nodosa, cortisol, corticosteroid analogs, colchicine, methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs), leflunomide, etanercept, minocycline, cyclosporine, thalidomide, a cytotoxic agent, 6-mercaptopurine, azathioprine, antibiotics or one or more of the proteins listed below.

The above paragraph recites that therapy can be administered following detection of the wound, wounded tissue, inflamed site or inflammatory tissue, and identifies exemplary drugs and compounds for treatment and also indicates that therapeutic proteins can be encoded by the microorganism or cell. Therefore, the specification, as filed, provides basis for claim 35.

Basis also is present in the specification as originally filed for claim 39. For example, the specification, at page 13, paragraph [0047], exemplifies how atherosclerotic plaques are imaged by targeting microorganisms or cells to the plaques, then treated by standard therapies or by modifying the microorganisms or cells to include a therapeutic agent, such as a plaque-destroying enzyme. Therefore, neither claim 35 nor claim 39 includes new matter.

VI. REJECTION OF CLAIMS 33-47 AND 51-80 UNDER 35 U.S.C. §112, FIRST PARAGRAPH - ENABLEMENT

Claims 33-47 and 51-80 are rejected under 35 U.S.C. §112, first paragraph, as being broader than the enabling disclosure. The Examiner urges that the claims are directed to a variety of subjects, tissues, diseases, cells, microorganisms and detection methods, and that the teachings of the specification and working examples are insufficient to practice the breadth of the embodiments encompassed by the claims. The reasons given by the Examiner are rebutted in turn below. This rejection respectfully is traversed.

Relevant law

To satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to

use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of §112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." *In re Marzocci et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." *In re Grimme, Keil and Schmitz*, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the subject matter *as claimed.* A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

Analysis

Summary of Arguments

As established below, the instant claims are directed to methods that employ bacteria that are detectable or that induce a detectable signal and that can be administered to subjects. The bacteria are administered to a subject. It is shown in the application that bacteria that are non-pathogenic and recognized by the immune system accumulate in any wounds, wounded

tissues, inflammation sites or inflamed tissues. The bacteria are either inherently detectable, such as heavy metal accumulating bacteria, or are modified to include a detectable product or to encode products and substrates to produce or induce a detectable signal. Such detectable products and signals are well known. Methods for detecting such bacteria in subjects are known and also described in the application.

Bacteria that can be administered and that are non-pathogenic and recognized by the immune system are known, and exemplified and described in the application. Such bacteria, not only are known and exemplified, they also can be prepared, as taught in the application, for detection of wounds/inflamed tissues/sites. Thus, the instant application provides a new use and method using known materials and detection/visualization methods. The use of bacteria and their accumulation in tumor tissues is known in the art. The instant application shows that such bacteria and detection/visualization methods can be employed to detect wounded/inflamed tissues.

As recited in the claims, the bacteria are not any bacteria but are (a) detectable; (b) non-pathogenic or attenuated; and (c) recognized by the immune system of the subject. The specification teaches numerous species of bacteria suitable for practice of the method and how to identify other species, the specification includes several working examples, with a variety of bacterial species, and teaches of the properties of bacteria for use in the methods. Those of skill in the art, who have a high level of skill, know of such bacteria and how to employ them for administration and visualization. Visualization/detection methods are known to those of skill in the art and also are described in the specification. Further, the specification demonstrates that the method is reproducible (*i.e.*, predictable). Thus, based on these factors, the factors enumerated in *In re Wands*, which include the scope of the claims, the teachings and examples in the specification, level of skill in the art, knowledge of those of skill in the art and state of the prior art, and predictability, it would not require undue experimentation for one of skill in the art to practice the methods as claimed to introduce detectable bacteria into a subject for the detection of a wound, wounded tissue, inflammation or inflamed tissue.

1. Breadth of the claims

Claim 33 recites:

> A method for detecting the presence or absence of a wound, wounded tissue, an inflammation site or inflamed tissue, comprising:
>
> administering to a subject a bacterium, wherein the bacterium encodes a detectable protein or a protein that induces a detectable signal;

monitoring the subject to detect the detectable protein or signal to detect accumulation of the bacterium at any wound, wounded tissue, inflammation site or inflamed tissue in the subject, thereby detecting the presence or absence of a wound, wounded tissue, an inflammation site or inflamed tissue in the subject, wherein:

the subject is one who is being evaluated for the presence or absence of a wound, wounded tissue wound, an inflammation site or inflamed tissue;

the bacterium is non-pathogenic or attenuated;

the bacterium is recognized by the immune system of the subject; and

the bacterium replicates in the subject.

Dependent claims recite particulars of the method, including the route of administration, exemplary bacterial species.

The claims are tailored to the teachings in the specification. Applicant is entitled to claims that are commensurate in scope not only with what Applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicant has disclosed. In the instant application, Applicant discloses to the public methods and compositions for the detection of a wound, wounded tissue, an inflammation site or inflamed tissue using known bacterial species that are detectable and known for detection by known methods. Applicant's contribution is the new use for the bacterium, detection wounded/inflamed tissues or sites. The specification clearly shows that bacteria with the properties recited in the claims accumulate at such sites and can be detected at such sites.

2. Level of Skill in the Art

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, further evidences the high degree of skill in this art.

3. State of the Prior Art

At the time of filing of the application, a broad body of knowledge had amassed in the areas of microbiology, molecular biology, genetics, and medicine including many technical procedures covering the generation, preparation, administration and detection of bacteria, viruses, and cells, including production of recombinant organisms using recombinant nucleic acid techniques, and expression and detection of exemplary detectable proteins, which are employed in the claimed methods. Numerous such procedures are referenced in the specification and/or described in the application and/or described in prior art submitted by Applicant to the Patent Office in connection with the instant Application.

The art provides numerous species of microorganisms that can be used in the methods provided in the instant application. The art provides bacteria that can be administered, including attenuated or non-pathogenic bacteria. For example, Pawelek *et al.* (WO 96/40238) provides numerous examples of attenuated or non-pathogenic bacteria and other microorganisms that can be administered to mammalian subjects (see Table 1 of WO 96/40238). The reference provides techniques for attenuation of the bacteria and methods for engineering the bacteria to express heterologous genes. Also provided are methods for selection of suitable bacteria for administration.

Numerous detectable proteins were known in art at the time of filing that can be used in the claimed methods. Exemplary detectable proteins include luminescent or fluorescent proteins, such as luciferase from *Vibrio harveyi* (Belas *et al.*, *Science* 218 (1982), 791-793) and from *Vibrio fischerii* (Foran and Brown, *Nucleic Acids Res.* 16 (1988), 177), firefly luciferase (de Wet *et al.*, *Mol. Cell. Biol.* 7 (1987), 725-737), aequorin from *Aequorea victoria* (Prasher *et al.*, *Biochem.* 26 (1987), 1326-1332), Renilla luciferase from *Renilla reniformis* (Lorenz *et al.*, *PNAS* USA 88 (1991), 4438-4442) and green fluorescent protein from *Aequorea victoria* (Prasher *et al.*, *Gene* 111 (1987), 229-233).

Techniques for construction light-emitting bacteria were known at the time for filing of the instant application. For example, bacteria engineered to carry the *lux-cdabe* operon for expression of bacterial luciferase and administration methods for infecting mice with such bacteria were well-known. Meighen and Szittner, *J. Bacteriol.* 174 (1992), 5371-5381 and Lee *et al.*, *Eur. J. Biochem.* 201 (1991) 161-167, Fernandez-Pinas and Wolk, *Gene* 150 (1994), 169-174, describe the lux operon and construction of a wide variety of bacteria that contain the operon for expression of the bacterial luciferase.

Expression of detectable proteins by microorganisms for detection of microorganisms within other organisms are described in the art and include, for example, expression of luxAB in *Rhizobia* residing within the cytoplasm of cells of infected root nodules (Legocki *et al.*, *PNAS* 83 (1986), 9080-9084; O'Kane *et al.*, *J. Plant Mol. Biol.* 10 (1988), 387-399), *Bacillus subtilis* and B*acillus megatherium* expression of lux A and lux B fusion genes (Fab2) in insect larvae and worms (Escher *et al.*, *PNAS* 86 (1989), 6528-6532), and *Pseudomonas* or *Ervinia spp.* expression of pathogen-activated PAL promoter-bacterial luciferase fusion gene in transgenic Arabidopsis plants, tomato plants and stacks of potatoes (Giacomin and Szalay, *Plant Sci.* 116 (1996), 59-72). Furthermore expression of light-emitting bacteria in mammalian subjects is described in Contag *et al.*, *Mol. Microbiol.* 18 (1995), 593-603.

Methods for detection of microorganisms, such as bacteria, that express light-emitting molecules were also known at the time of filing. For example, luminescent and fluorescent signals produced by such proteins can be detected with low light imaging cameras or fluorescent imaging devices (Engebrecht *et al.*, *Science* 227 (1985), 1345-1347; Legocki *et al.*, *PNAS* 83 (1986), 9080-9084; Chalfie *et al.*, *Science* 263 (1994), 802-805).

Contag *et al.* (U.S. Patent No. 6,217,847) describes methods of *in vivo* imaging, including bacteria and viruses that express detectable proteins. The reference describes administration of light-emitting bacteria and provides working examples of intraperitoneal administration of bioluminescent *Salmonella*. The reference also provides numerous examples of light-emitting proteins that can be expressed by the bacteria (see, *e.g.* columns 9-10) and methods of detecting the bacteria including several types of photodetection and amplification devices (see, *e.g.* columns 16-17). In addition, the reference also provides a detailed description of the methods that can be employed to image the bacteria *in vivo* (see, *e.g.* columns 17-20).

Zhao et al. (2001) *PNAS* 98(17) 9814-9818 describes methods of engineering GFP-expressing *E. coli* for *in vivo* detection. Methods for preparing, administering and detecting the bacteria *in vivo* are provided. The reference describes a method of tracking the fluorescent signal emitted by the bacterium in a live animal over time. The reference thus describes methods of spatial and temporal imaging of bacterial localization within a subject.

In addition, techniques and methods for expression and *in vivo* detection of fluorescent and bioluminescent molecules can be found in Belas *et al.*, *Science*, 218: 791-793 (1982), Chalfie et al, *Science* 263: 802-805 (1994), Contag *et al.*, *Mol. Microbiol.* 18: 593-603 (1995), Greer III, L.F. and A.A. Szalay, *Luminescence.* 17(1):43-74 (2002), Rodriguez, J.F. *et al.*, *PNAS* U.S.A., 85: 1667-1671 (1988), Rocchetta *et al.*, *Antimicrobial Agents and Chemotherapy* 45(1): 129-137 (2001), Yang *et al.*, *PNAS* 97(22): 12278-12282 (2000), Wang Y. *et al.*, *Mol Genet Genomics.* 268(2):160-8 (2002), Lamberton *et al.*, *Proceedings of the 12th International Symposium on Bioluminescence & Chemiluminescence:* 5-9 April 2002, Robinson College, University of Cambridge, UK, p 3.22 (2002)

Techniques and methods for use of other detectable molecules for *in vivo* labeling such as radionucleotides for MRI or PET imaging can be found in Welling *et al.*, Eur J Nucl Med. 27(3):292-301 (2000), Adonai *et al.*, *PNAS* USA 99: 3030-3035 (2002), Welling *et al.*, *Nucl Med Biol.* 29(4):413-22 (2002), Nibbering *et al.*, Nucl Med Commun. 19(12):1117-21 (1998), Weissleder, T. *et al.*, *Nat. Med.* , 6(3): 351-354 (2000), Berger, F. and S.S. Gambhir,

Breast Cancer Research 3: 28-35 (2001) (Additional references and imaging techniques can also be found in pre-filing date references cited in Massoud *et al. Genes & Development* 17: 545-580 (2003).

The references cited above are not an exhaustive list of the references that were available to one of skill in the art at the time filing. They are a representative selection of art to demonstrate the existence large volume of information regarding tested and reliable procedures available at the time of filing of the instant application and thus evidence the advanced state of the art at the relevant time with regard to known methods of methods of selection of, modifying, administering and detecting microorganisms and cells, including bacteria and viruses. They evidence the advanced state of the art with respect to identification of bacteria with properties recited in the claims, and methods for detection/visualization.

Rebuttal to Examiner's argument that Yu *et al.* (2003) demonstrates that the Art is not enabling of the breadth of Applicant's claims

While further rebuttal to the Examiner's comments are set forth below, it is pertinent to discuss the Yu *et al.*, cited by the Examiner on pages 14 and 15 of the Office Action. Examiner maintains that Yu *et al.* (2003) demonstrates Yu *et al.* demonstrates that bacteria, viruses or mammalian cells, when administered to subjects, accumulate in cancerous tissues, but not in any tissue recited in the claimed subject matter. The Examiner further alleges that Yu *et al.* teaches that the mechanism of bacterial colonization is unknown, that administration type-dependent colonization is common and that it is not "predictable" which administration will yield which colonization type.

First, Yu *et al.*, employs tumor models, **not** inflammation/wound models, and shows that bacteria accumulate in tumorous tissue. Yu *et al.* does not show anything regarding wounded or inflamed tissues/sites. Yu *et al.*, which published post-filing date, describes methods of detection of tumors. Hence, it is not pertinent to the methods of the instant claims. Therefore, the Examiner's statement that Yu *et al.* is not enabling of the claimed subject matter, is inapt, since Yu *et al.* is directed to different subject matter and is published subsequent to the priority date of the instant application. Yu *et al.*, is irrelevant to whether or not the application teaches how to make and/or use the claimed method, which is for detecting wounds/inflamed tissues.

Second, knowledge of the mechanism of colonization or colonization-type is irrelevant to the practice of the methods as claimed. By following the teachings of the

specification, the bacteria are administered, and, as taught and demonstrated in the application, bacteria, with the recited properties, accumulate at wounded/inflamed tissues/sites. The teachings of the specification, in light of the state of the art and the knowledge of those of skill in the art, allow one of skill in the art to practice the steps of the methods as claimed. Knowledge of the mechanism of localization or the types of colonies visualized at the sites of localization, is not needed. The specification teaches and demonstrates that bacteria that are recognized by the immune system and that are nonpathogenic or attenuated accumulate at such sites/tissues.

4. Nature of the Claimed Subject Matter

The claimed subject matter is a method for detecting wounds, wounded tissues, inflammation sites, inflamed tissues by administration of bacteria that are non-pathogenic and recognized by the immune system. The application teaches and demonstrates and exemplifies that such bacteria accumulate in such tissues/sites. As discussed above, the claims are directed to methods of use of known materials that can be detected/visualized by known methods. Hence, the scope of the reagents used in the methods and the detection methods should not be at issue. Once Applicant describes the use of such reagents for detection of wounds/inflamed tissues/sites, more should not be needed for one of skill in the art to practice the methods as claimed.

5. Predictability of the method

The specification provides three working examples with three different species of bacteria, and shows that all, as described in the specification accumulate wounded and inflamed tissues/sites. All three exemplified species p accumulated in wounded and inflamed tissues. The data show that an animal with a wounded or inflamed tissue/site can be administered an attenuated, non-pathogenic bacterium that is recognized by the immune system and the administered bacteria accumulates in the wounds or inflamed tissues/sites, thereby allowing detection of the wound. Practice of the method with other bacteria in addition to the exemplified species and detection methods should be routine, since the claims and specification recite the properties of the bacteria required, including that they are non-pathogenic and recognized by the immune system, and as demonstrated those of skill in the art can readily identify other such bacteria and detection/visualization methods based upon their knowledge, the art and/or the teachings in the specification. As described above, a variety of non-pathogenic or attenuated bacteria recognized by the immune system were known at the time the priority date, as were methods for detection thereof for visualization of

tissues/sites as described above (see references discussed above, and the specification as discussed herein). Hence there is no basis to conclude that successful practice of the method is not predictable.

Rebuttal to Examiner's argument that the Artisan would not reasonably predict that any microorganism would accumulate in any of the tissues claimed

On page 16 of the Office Action, the Examiner alleges:

> With regard to the microorganism which may be administered, the Artisan would not reasonably predict that any microorganism would accumulate in any of the tissues claimed. To wit, for example, a bacteriophage cannot even infect eukaryotic cells, and hence would not reasonably be predicted to accumulate anywhere except the liver.

First, the pending claims are not directed to any microorganism, but to bacteria that are non-pathogenic and that are recognized by the immune system. Further, the specification, teaches a variety of such bacteria, and, as discussed above, those of skill in the art are familiar with such bacteria. Further, the specification exemplifies three species and teaches others; and those of skill in the art familiar with other such species (see, *e.g.*, the art discussed above).

Second, the Examiner has not provided any evidence to support the assertion that a microorganism, such as a bacteriophage, would not, in fact, localize to a wound, wounded tissue, inflammation site or inflamed tissue. The specification demonstrates the opposite. The Examiner cannot take judicial notice of such fact and should provide basis for such supposition. Judicial notice cannot be taken unless the facts are capable of "instant and unquestionable demonstration," which the contradictory "facts" alleged by the Examiner are not.

The Examiner is reminded that MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well-known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..

Applicant respectfully submits that it is not "unquestionably demonstrable" that bacteriophage cannot localize to a wound, wounded tissue, inflammation site or inflamed tissue. Also, to the Applicant's knowledge, there is no evidence that bacteriophage do not accumulate in wounded or inflamed tissues. Furthermore, Examiner states on page 20 of the Office action, "it is a truism that bacteriophages do not infect eukaryotic cells." Applicant respectfully submits that at the time of filing, techniques were readily available to one of skill

in the art to employ bacteriophages to transfer nucleic acid to mammalian cells (see, for example, Larocca *et al.* (1999) *FASEB J.* 13: 727-734, which is provided with the Information Disclosure Statement filed under separate cover). Hence, there is no evidence that bacteriophages would not predictably localize to a wound, wounded tissue, inflammation site or inflamed tissue and infect cells for the expression of a detectable protein as taught by the specification.

6. Amount of Direction and Guidance Provided by the Specification

The specification describes the generation, administration, and detection of microorganisms and cells for the detection of a wound, wounded tissue, an inflammation site, inflamed tissue, or a disease or condition associated thereof. The teachings of the specification describe how to select an organism or cell for use in the methods, how to administer the microorganism or cell, how to detect the microorganism or cell *in vivo*, and provides instruction on how to modify the microorganism or cell for diagnosis or therapy. The specification also provides guidance as to the selection of features of microorganisms or cells for use in the methods of detection (*e.g.*, non-pathogenic or attenuated, recognition by the immune system). It is taught that such detection is useful for visualization of and diagnosis of the wounded or inflamed tissues and for therapy of the wounded or inflamed tissues, including identification of site for subsequent application of a therapeutic agent (paragraph [0024]) or directed expression of proteins suitable for therapy at the affected site.

The specification teaches examples of proteins that can be expressed by the microorganism or cell for diagnosis and treatment (paragraph [0025]). For example, diagnostic proteins, such as fluorescent, bioluminescent, and metal binding proteins (see, *e.g.*, paragraphs [0029], [0033]-[0037]) and therapeutic proteins, such as various growth factors and enzymes (see, *e.g.*, paragraphs [0026]-[0037]) can be expressed by the microorganisms or cells and are described. Exemplary vectors including viral, mammalian and bacterial vectors for the expression of such proteins are also exemplified (see, *e.g.*, paragraphs [0023] and [0031]).

The specification teaches exemplary microorganisms and cells that can be used in the claimed methods including bacteria, such as attenuated *Salmonella typhimurium*, attenuated *Vibrio cholera*, attenuated *Listeria monocytogenes*, or *E. coli*, and viruses such as a Vaccinia virus, an adeno-associated virus (AAV), or a retrovirus (paragraph [0038]).

The specification further teaches methods of administering the microorganism or cell, including routes of administration and factors to be considered for assessing methods of

administration and dosages (see, *e.g.*, paragraph [0045] and the Examples). The specification also provides examples of diseases and conditions that are associated with wounded or inflamed tissue that can be used in the methods for diagnosis and treatment (see, *e.g.*, paragraphs [0046]-[0048]). Also provided are examples of combination therapies that can be employed with the microorganisms or cells, including administration of therapeutic proteins and molecules (see, *e.g.*, paragraph [0049]).

7. Working Examples

The specification provides working examples and descriptions of the generation, administration, and detection of microorganisms and cells for the detection of a wound, wounded tissue, an inflammation site or inflamed tissue. The working examples of bacterial accumulation at wounded or inflamed sites provide sufficient teachings, in combination with what was known to those of skill in the art at the time of the instant application's earliest priority date, to generate, administer, and detect a microorganism or cell regardless of the microorganism or cell that is used provided that the microorganism or cell is detectable. For example, techniques for use in the administration and detection of luminescent bacteria in an animal model for wounded tissues are provided in Examples 1, 2 and 3, including examples of plasmid constructs that can be used for bacterial expression of bacterial luciferase, administration methods (*e.g.* intravenous injection), methods and equipment employed for detection, and methods for generating wounded tissue for the experiment, including incision wounds, ear tags wounds, and surgical heart defects. Such techniques are applicable to use of the methods in subjects with existing wounds or inflamed tissues. Furthermore, the examples provide guidance for one of skill in the art to create animal models for testing particular detectable microorganisms and cells. For example, methods and instruction were provided for analysis of accumulation in wounded/inflamed tissue versus unaffected tissue in an animal model, including whole body luminescence detection as well as organ excision and cell culture methods for analyzing various tissues of the animal model.

The working examples exemplify the teaching using three diverse species of bacteria (*S. typhimurium*, *V. cholera*, and *E. coli*). Each of these bacteria were modified to express a protein that induces a detectable signal, a bacterial luciferase, which is expressed from the *lux-cdabe* operon. Also expressed from the *lux-cdabe* operon are proteins involved in the production of the substrate for the luciferase, which allows detection of the bacteria. The examples demonstrate exemplary methods of systemic administration of the microorganisms by intravenous administration. Following intravenous administration, the bacteria are

initially carried throughout the body via the blood stream as shown in Figure 1. After a period of time, both *S. typhimurium* and *V. cholera* were shown to accumulate in cutaneous wounds and inflamed tissues of the ear (Example 2). In Example 3, *E. coli* was shown accumulate in wounded heart tissue. In all cases, the bacteria was efficiently cleared from non-wounded tissues by either the subject's immune system or organs normally involved in bacterial clearance, such as the liver and spleen. Given the normal function of the liver and spleen in bacterial clearance, initial accumulation of bacteria in the liver and spleen was observed in some instances.

The specification teaches that these are exemplary and that the examples can be extrapolated and use for any species. Further, Applicant is not required to provide data or illustrative examples in support of every embodiment within the scope of a claim. *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973)).

8. Quantity of Experimentation

The type and quantity of experimentation in light of the teachings of the specification and knowledge and skill of those in the art is routine. As discussed above, the specification teaches the properties of bacteria for use in the methods and exemplifies the methods with three different species. Those of skill in the art are familiar with other suitable species, as well as detection/visualization methods. Accordingly, any experimentation with different species would be routine to confirm, if necessary, that a particular species is accumulates in wounded/inflamed tissues, and optimization of parameters for such species. The specification teaches and exemplifies how to test species and parameters to optimize.

As evidenced by the state of the art discussed above, any needed manipulations to prepare bacteria have been practiced for many years. Furthermore, detection techniques for *in vivo* detection and methods to optimize such techniques are also well known. The application also provides ample guidance for routine testing of a microorganism or cell for use in diagnosis or treatment of wounded or inflamed tissues. Applicant notes that "a considerable amount of experimentation is permissible, if it is merely routine..." *In re Wands* 858 F.3d 731, 737.

Conclusion

Therefore, in view of the breadth of the claims, the high level of skill of those in the art, the knowledge of those of skill in the art, the teachings in the prior art, the teachings in the application, the working examples in the application, and the demonstrated repeatability

of the method as claimed, it would not require undue experimentation to practice the methods as claimed. Thus, the claims are enabled and are not broader than the enabling disclosure.

REBUTTAL TO THE EXAMINER'S ARGUMENTS

a. Rebuttal to Examiner's argument that colonization is bacterial-strain dependent and administration dependent

On page 16 of the Office Action, the Examiner alleges:

> Applicant has stated in the specification that even the bacteria used to infect the rats used have distinct interactions with the host cell (paragraph 0061), and the distribution pattern of any particular bacteria is not reasonably predictable, being bacterial-strain dependent (paragraph 0060) and moreover, the particular distribution patterns depends on the method of administration (paragraph 0045).

First, Applicant is making of record the fact that that the following two statements attributed to Applicant in Office Action are statements made by the Examiner and not by the Applicant: These statements made by the Examiner are: "the distribution pattern of any particular bacteria is not reasonably predictable" and "the particular distribution patterns depends on the method of administration." Neither statement was made by Applicant.

As discussed above, and shown in the application, bacteria for use in the methods are known, and the methods for detection of the bacteria are known. As discussed above, the bacteria and means for detection/visualization are known reagents that can be used in the instantly claimed methods. The application teaches that bacteria accumulate in wounds/inflamed tissues/sites and demonstrates that with working examples using three different strains. There is no basis for the Examiner to conclude that other strains known to have the properties recited in the claims do not accumulate in wounds/inflamed tissues/sites. Further, if needed, one of skill in the art can test a candidate strain that meets the recited criteria exactly as taught in the specification to confirm that the strain accumulates. No knowledge of the mechanism for accumulation is needed. Further as described above, detection/visualization methods are known to those of skill in the art and also are described in the application. One of skill in the art can employ any such method.

The Examiner has cited statements set forth in paragraphs [0060] and [0061] of the specification to support the argument that the distribution pattern of any particular bacteria is not reasonably predictable. Despite the fact that the distribution pattern of any particular bacteria can be readily tested, the cited sections and accompanying working examples show that regardless of any differences in distribution profiles or kinetics, **the tested microorganisms consistently localized at sites of inflammation, injury or disease.**

The particular sections of paragraphs [0060] and [0061] of the specification that are set forth above reference statements taken out of context of the experiment described in Example 2. The statements describe the initial observation period only (0-60 minutes) for the experiment. As described in the specification, the experiment involves the injection of attenuated *Salmonella typhimurium* and attenuated *Vibrio cholerae* (each carrying the pLITE201 plasmid for expression of bacterial luciferase) into the left femoral vein of anesthetized mice. Prior to the injection, the left femoral vein was exposed by making a 1 cm incision with a surgical blade. Following injection of the bacteria, the incision was closed with 6-0 sutures, and the mice were then monitored under a low light imager for photon emission. The results for the initial distribution of the bacterial strains following injection into the mice were shown in Figure 1 of the application and described in Example 2. As stated in the paragraph [0060] of the specification:

> Injection of attenuated S. typhimurium caused wide dissemination of the bacteria throughout the body of the animals (FIG. 1A). This pattern of distribution was visible within 5 minutes after bacterial injection and continued to be detected at the one-hour observation period. Injection of attenuated V. cholera into the bloodstream, however, resulted in light emission that was localized to the liver within 5 minutes after bacterial injection and remained visible in the liver at the one-hour observation period (FIG. 1B).

The difference cited by the Examiner for localization of the two bacteria in this experiment refers to the initial observation period where *V. cholera* was seen to localize to the liver and S. *typhimurium* was more widely distributed throughout the animal. One of the primary functions of the liver, widely known at the time of filing of the application, is to clear toxins and foreign materials from the bloodstream. Thus, it is not surprising that injected bacteria would accumulate in the liver soon after injection. Given what was widely known about the liver at the time of filing, one of skill in the art **would not interpret** this initial localization to the liver at five minutes post-injection of the bacteria to indicate that the liver is a site of a wound, wounded tissue, inflammation site or inflamed tissue. Regardless of any reasons why the bacterial strains may have differed in their accumulation in the liver during the initial observation period, this difference had no impact on the results of the experiment, in which both strains exhibited accumulation in the wounded and inflamed tissues after clearance of the initial wave of distribution as shown in Figure 2.

It respectfully is submitted that the statement in paragraph [0061] that "the distribution pattern of light emission following an intravenous injection of bacteria into the

mice was bacterial-strain-dependent" should not be taken out of context of the experiment as a whole. The statement refers only to the initial observation period of the experiment and has no bearing on the outcome, namely, both bacterial strains accumulated in the wounded/inflamed tissues and not in uninjured tissues. This was clearly shown in Figure 2 as well as stated in paragraph [0061]:

> Imaging the same animals 48 h after bacterial injection showed that **all** of the detectable light emission from the earlier time had diminished and was eliminated completely from the injected animal with the exception of the inflamed wounded tissues such as the incision wound and the ear tag region...Careful examination of individually excised organs as well as blood samples from infected animals confirmed the absence of luminescence in these normal uninjured tissues."[emphasis added].

Hence, the Examiner's assertion regarding the difference in the distribution among the bacterial strains has no bearing on the ability of both tested strains to accumulate in wound/inflamed tissues, as supported by the Examples.

With respect to paragraph [0045] mentioned above, the Examiner asserts that "the particular distribution patterns depends on the method of administration." No such admission is made by Applicant. Paragraph [0045] of the specification teaches that the microorganisms or cells can be administered using different routes "*e.g.* by intravenous, intraperitoneal, subcutaneous, intramuscular, topical or intradermal administration." Applicant states in paragraph [0045] that:

> The route of administration, of course, depends on the nature of the tissue and the kind of microorganisms or cells contained in the pharmaceutical composition. The dosage regimen will be determined by the attending physician and other clinical factors. As is well known in the medical arts, dosages for any one patient depends on many factors, including the patient's size, body surface area, age, sex, the particular compound to be administered, time and route of administration, the kind and localization of the tissue, general health and other drugs being administered concurrently.

Although the route of administration can depend on the kind of microorganisms or cells contained in the pharmaceutical composition, the cited passage clearly teaches that selection of an appropriate route is a matter of routine, given the advanced state of the art with respect to administering microorganisms or cells to subjects. The cited passage in no way implies that the route of administration would affect the ability of the microorganisms or cells to localize to wounded, diseased or inflamed sites as taught by the methods of the specification. Instead, the specification merely states that particular routes of administration may be better suited for detection of a particular wounded or inflamed tissue. As discussed above, factors for determining the preferred route of administration based on the type of

wound or inflamed tissue are taught by the specification and are known to those of skill in the art. Furthermore, as discussed above, one of skill in the art would possess the knowledge needed for assessing such factors for determination of an administration route and dosage.

b. Rebuttal to Examiner's assertion that initial accumulation in the liver falsely indicates a wounded or inflamed tissue

On page 16 of the Office Action, the Examiner states that "by Applicant's method, if a rat was unaffected, accumulation in the liver would indicate that the liver had a wound, inflammation, and coronary artery disease." It respectfully is submitted that this statement is incorrect. As argued above, one of skill in the art would be aware of the function of the liver to cleanse foreign matter from the bloodstream. As such, if the bacteria were administered such that the bacteria were deposited into or had access to the blood stream (*e.g.* by intravenous administration), it would not be surprising to observe accumulation in the liver. Hence, one of skill in the art would not interpret this initial accumulation in the liver as an indication of a wounded or inflamed tissue.

Furthermore, the specification teaches the kinetics of targeting and clearance of the microorganisms from the non-wounded or non-inflamed tissues. Thus, one of skill in the art would be able to distinguish whether the accumulation of the microorganisms or cells is the result of toxic clearance or accumulation at a wounded or inflamed tissue.

c. Rebuttal to Examiner's assertion regarding accuracy of the method

The Examiner argues that the method is accurate "at best, only 41.4% of the time (paragraph [0061])" and that:

> Applicant may argue that 82.8% of the injection wounds also showed such colonization, but such may also be explained by the fact that such is where the bacteria was present in high concentration, and hence, it would not be reasonably predictable for non-injection wounds, and therefore would require undue experimentation for the breadth to make it so-predictable."

Applicant respectfully disagrees with the Examiner's conclusion and interpretation of the experiment presented in Example 2. The Examiner has failed to take into account that the bacteria were widely dispersed throughout the animal or found in the liver and not at the inject site **immediately** following injection (as shown in Figure 2 and Figure 3). As such, there was not a disproportionate concentration of bacteria at the injection site at time points soon after injection. The accumulation of light emitting bacteria at the site of incision was gradual and accompanied by complete disappearance of the light emitting bacteria from sites

other than the wounded/inflamed tissue after 2 days. Although the percentage of bacterial wound accumulation was less at the sites of ear tag wounds (41.1%), the accumulation that did occur was clearly detectable compared to non-wounded/inflamed tissues. The lower accumulation could reflect a difference in the level of inflammation at the site of the individual ear tags; it is not a reflection of the accuracy of the method as asserted by the Examiner. In fact, the result that the bacteria did not accumulate in non-wounded or non-inflamed tissues following the initial observation period for both strains tested further demonstrates the success of the method.

Notwithstanding the arguments above, Applicant respectfully submits that a particular level of efficacy is not required to demonstrate that the method is enabled. Methods of optimizing a regimen to achieve higher colonization levels for a particular microorganism or cell would not be considered undue experimentation. Further, the Examples demonstrate that by following the teachings of the specification one of skill in the art can use the method to administer a microorganism or cell to a subject with a wound or inflamed tissue and can detect accumulation of a microorganism or cell at a wounded or inflamed tissue and thereby the wounded/inflamed tissue/site without undue experimentation.

d. Rebuttal to Examiner's argument regarding enablement of the detection techniques encompassed by the claims

On page 17 the Office Actions states:

> the specification only discloses fluorescent proteins, for detection by light emission, and by MRI.. However, Applicant's claims encompass any detection method. However, given that Applicant wishes to detect these tissues, the method would not be one which causes any damage to the organism itself, because, according to the method, the microorganism/cell would accumulate in the damaged tissue, and provide false readings, it would appear that the only methods of detection are by MRI or fluorescence detection.

In the previous response, submitted on December 13, 2006, Applicant argued that the Examiner is required to do more than just categorically state that some of the detection methods "may" damage tissues. In response, the Examiner proposes two detection methods that damage tissues. On page 22 of the Office action, Examiner states,

> The detection methods may be to extract the tissue, chop it up, and detect the DNA or mRNA therefore, thereby detecting the tissue. Another method would be to cut open the tissue and see a marker protein, such as beta-galactosidase, change the color of X-gal. However, the processes necessarily damages the tissue, and hence, demonstrate there will be colonization of the method claimed.

With respect to the Examiner's first example, Applicant submits that the pending claims are directed to detecting the presence or absence of a wound, or wounded tissue, an inflammation site or inflamed tissue **in** the subject. Hence, the tissues are not extracted.

With respect to the Examiner's second example, Applicant respectfully submits that any person, with or without skill in this art, would know that cutting open a subject causes damage to the tissues surrounding the incision. The specification, however, bacteria that are non-pathogenic or attenuated and recognized by the immune system accumulate in such damaged tissues, thereby demonstrating and exemplifying the working method. Such wounds are a model system for demonstrating the methods. As Applicant has previously stated, in practice of the methods, detection techniques to visualize tissues are known and that methods that are not damaging are known. Detectable molecules, such as fluorescent molecules, for example, are known in the art to not cause damage to the host, and would be suitable molecules that one of skill in the art would select for detection (see Hoffman (1999) *Methods Enzymol.* 302:20-31). The Examiner has not provided any evidence to suggest that such detection methods would necessarily damage tissue, thereby causing bacteria to accumulate in the tissue, without the Artisan knowing that he damaged the tissue. In fact, the specification, teachings in the art and knowledge of those of skill in the art indicate otherwise.

The claims recite that the bacteria non-pathogenic or attenuated so that they do not damage the subject. This fact, and also the extensive knowledge and skill of those of skill in the art and the fact that detection/visualization methods are known, permits practice of the methods without damaging tissues. Again the Examiner has taken judicial notice of facts outside the record, and facts that contradict what is taught and demonstrated in the application.

Furthermore, Applicant respectfully disagrees with the Examiner's assertion that the only methods of detection of the microorganisms or cells taught by the specification are by MRI or fluorescence detection. Limiting the claims two methods of detection is unduly limiting for the practice of the claimed methods, since those of skill in the art could readily avoid claims so-limited and employ other detection/visualization methods and practice the methods disclosed in the application. The Examiner's statement that "the specification only discloses fluorescent proteins, for detection by light emission, and by MRI" is incorrect. The specification teaches numerous examples of proteins that can be used for detection in the claimed method that are not fluorescent proteins. For example, the specification discloses

various luminescent proteins, such as bioluminescent proteins (*e.g.*, luciferases), which are not fluorescent proteins. By definition, a fluorescent protein requires incident light in order to fluoresce or emit light, whereas a luciferase catalyzes the oxidation of a substrate molecule in order to emit light. Further, the bacterial strains employed in the Examples contain a *lux-cdabe* cassette, which allows for the expression of a bacterial luciferase. In addition, those of skill in the art are familiar with a variety of detectable proteins and detectable inducible (or producible) products.

The specification provides additional examples of detection including use of metal binding proteins or proteins that can bind a contrasting agent, chromophore, or compounds. One of skill in the art at the time of filing of the instant application, and as of its earliest priority date, would understand that a compound that binds to protein can be, for example, a radiolabeled compound or a compound that contains a paramagnetic ion, or produces ultrasound echoes. As such, the compound when bound to the microorganism or cell, can be detected by a variety of methods known to those of skill in the art as of the application's earliest priority date including magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission tomography (SPECT), X-ray computed tomography (CT), ultrasound. Examples of such compound and detection methods were all available and known to one of skill in the art at the time of filing and as of the earliest priority date as described above.

As discussed above, to demonstrate the full scope of enablement of the claimed methods, Applicant is not required to demonstrate a completely optimized procedure as long as it is possible to successfully perform the method as claimed without undue experimentation. Contrary to the assertion of the Office Action, the ability to practice the methods as claimed is not dependent on the particular bacterium that is used in the method. Instead the non-pathogenic or attenuated microorganism or cell is a tool that is used to detect abnormal conditions in a subject, such a wound or inflamed tissue, a foreign object (*e.g.*, a suture), or a disease or condition associated with wounded or inflamed tissue. It is not a characteristic of the particular microorganism or cell per se that provides for specific colonization of the wounded or inflamed tissue, but rather is the protective environment of the wounded or inflamed tissue (from the immune system) that leads to accumulation of bacteria in such sites. The bacteria administered are cleared by the immune system from non-wounded or non-inflamed tissues. Hence, any non-pathogenic or attenuated microorganism or cell that is recognized by the immune system should accumulate in wounded or inflamed

tissue as taught by the specification. The claimed methods are thus applicable to any non-pathogenic or attenuated microorganism or cell that is recognized by the immune system. Such microorganisms and cells will be cleared from most tissues/sites, but not from wounded/inflamed tissues/sites.

The Examiner has provided no basis for the conclusion that one of skill in the art would not have been able to practice the claimed method. The Examiner has stated on page 16 of the Office Action that "the Artisan would not reasonably predict that any microorganism or cell would accumulate in any of the tissues claimed." As noted above, the claims are not directed to any microorganism or cell, but to bacteria that are non-pathogenic or attenuated that are recognized by the immune system. (The claims, while not reciting microorganisms or cells also could include microorganisms or cells).

Further, on page 12 of the Office Action, the Examiner states, "Because of the art, as shown above, does not disclose enough to reasonably predict the working embodiments encompassed by Applicant's claim, the Artisan could not predict, in the absence of proof to the contrary, that such applications would [be] efficacious in any diagnosis." Examiner makes reference to "art, as shown above"; however, no art was shown other than Yu *et al.*, which, as demonstrated above, is not pertinent.

With regard to efficacy for diagnosis, the Examiner appears to set forth an argument for inoperability of the claimed method where no such rejection has been set forth in the Office Action. The working examples contradict any such argument.

Further, in order to practice the methods as claimed, it not required that a particular microorganism or cell achieve a minimum level of colonization at the site of the wounded or inflamed tissue as suggested by the Examiner on page 17 of the Office Action. Examiner states that the Artisan "may still only expect the method to be accurate, at best 41.4% of the time." It is respectfully submitted that the Examiner is equating the standard for enablement of the claimed subject matter with an established clinical therapy regimen. Such is not the standard for enablement or operability. (See, *e.g.*, MPEP §2164.05, Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) for the proposition that considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled. *See also*, for example, MPEP §2107.03, In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995) holding that FDA approval is not a prerequisite for finding utility within the meaning of the patent laws).

Applicant is not aware of any requirement under current U.S. patent law specifying particular minimum levels of optimization and certified efficacy in order for a treatment-related area of art to qualify as sufficiently "predictable" such that lack of enablement under 35 U.S.C. §112, first paragraph, is not a consideration. The relevant standard is not that of an established, fully optimized, clinical course of treatment; rather, even in an unpredictable art, a patent application satisfies the requirements of 35 U.S.C. §112, first paragraph, as long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of skill how to make and use the claimed subject matter with reasonable, but not undue, experimentation. There is no requirement that a method achieve a specified level of efficacy or efficiency in order to be considered "enabled" by the specification.

On page 22, the Examiner maintains that he is "not arguing for a level of efficacy, but that given what is demonstrated, the Artisan cannot reasonably predict the huge breadth encompassed." The Examiner has not provided any evidence to suggest that other microorganisms that are recognized by the immune system and that are nonpathogenic or attenuated would not accumulate at wounds/inflammation sites/tissues. The Examples demonstrate that different microorganisms do accumulate in wounded or inflamed tissues. .

It appears that the Office Action, in asserting the unpredictability of the claimed methods, has equated a fully established clinical or experimental regimen, uniformly applicable across every system, with "unpredictability." It is respectfully submitted that, as the references of record establish, microorganism or cells that are recognized by the immune system and that are nonpathogenic or attenuated in addition to than those in the application, can be administered to a subject, and, as further evidence by the disclosure of the application, detection of accumulation at a site of wounded or inflamed tissues can be achieved. It respectfully is submitted, that although the art of the use of microorganisms or cells for the purpose of detection or treatment of wounded or inflamed tissues was not known as of the effective filing date of the subject application (as this is Applicant's discovery), the specification provides working example demonstrating three different species of bacteria and showing that each accumulates in wounded/inflamed tissue. Further, species of bacteria that at are recognized by the immune system and that are nonpathogenic or attenuated that can be used in the are known to those of skill in the art, and hence, in view of the teachings in the specification, one of skill in the art, can now select other bacterial species to practice the methods.

Policy Considerations

As demonstrated by the above analysis of the *In re Wands* factors, the teachings of the specification, when combined with the knowledge of those of skill in the art and the ability to repeatedly and successfully (i.e., predictably) execute the various steps, leads to the conclusion that each of the steps of the instant methods could be performed without undue experimentation. As discussed above, administration of microorganisms for the detection of wounded or inflamed tissue was successfully demonstrated using a variety of microorganisms by following the teachings of the instant application and by an extensive body of knowledge in the art as of the application's earliest priority date.

Applicant is entitled to claims that are commensurate in scope, not only with what Applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicant has disclosed. In the instant application, Applicant provides the public with methods for the detection of a wound, wounded tissue, an inflammation site, inflamed tissue thereof by administering and detecting a variety of microorganisms or cells that accumulate at such sites. As a broad body of knowledge is available in the areas of microbiology, genetic manipulation of microorganisms and cells, administration of microorganisms and cells to subjects, and *in vivo* detection techniques for detecting the administered microorganisms and cells, it would be unfair and contrary to the Constitutional mandate set forth in Article, Section 8, require applicant to limit the claims to any particular embodiment or to deny patent protection at all. To do so would permit those of skill in the art to practice the methods as described in the application with any microorganism or cell, particularly any bacterial species and/or detection/visualization method that meets the recited criteria, and avoid infringing claims to which Applicant is entitled.

See, e.g., In re Goffe, 542 F.2d 801, 166 USPQ 85 (CCPA 1970).

> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions" In re Sus and Schafer, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

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